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INVITED COMMENTARY

Who's still afraid of the link between headache and epilepsy? Some reactions to and reflections on the article by Marte Helene Bjørk and co-workers

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I was delighted to be invited to comment on the article by Marte Helene Bjørk and co-workers entitled "Interictal quantitative EEG in migraine: a blinded controlled study", published in this issue of *The Journal of Headache and Pain* [1]. I was delighted for three reasons. Firstly, because this article makes a major effort to shed light on the inter-ictal cortical excitability changes using a quantitative EEG (QEEG) investigation in migraine-affected subjects. Secondly, because this commentary offers me the opportunity to stress the need to, respectively, define and revise criteria in both the International League Against Epilepsy (ILAE) classification and International Classification of Headache Disorders Second-Revision (ICHD-II). Indeed, to date neither the International Headache Society nor the International League against Epilepsy mention that headache/migraine may, on occasion, be the sole ictal epileptic manifestation. This is reflected in the ICHD-II criteria, both for the "hemicrania epileptica" classification (coded as 7.6.1) where you can see….in point B of criteria…. … "the patient is having a partial epileptic seizure"… and for "post-ictal headache" classification (coded as 7.6.2) where you can see in point B of criteria…. "the patient has had a partial or generalized epileptic seizure". Thirdly, *The Journal of Headache and Pain's* readers represent the most suitable audience with whom to share some recent contributions to this hot topic by our group [2–6]. I will thus focus on the main findings of this well-conducted study by Marte Helene Bjørk et al., and will conclude with some reactions to and reflections on our recent papers [2–6], which are, I feel, more closely related to the article commented on here than might appear at first glance.

Studies based on QEEG have previously been performed on childhood migraine, though the results were conflicting [7]. It is important to stress the considerable methodological (see study design) [1], contribution of this blinded controlled study by Marte Helene Bjørk et al. who, interestingly, evaluated EEG findings in migraineurs at a time when neither the previous attack nor the subsequent attack may have interacted with the results. The authors tackle a very important topic by comparing the quantitative inter-ictal EEG in migraineurs and headache-free subjects, investigating pre-ictal EEG findings on the painful cranial side after the subsequent attack has been recorded; particularly, all EEGs recorded during attack or within 36 h before and after migraine attack were excluded. Correlations between clinical variables and EEG were also investigated. On the basis of the increased theta activity they observed in migraineurs, they suggested a slight inter-ictal brain dysfunction in migraineurs between attacks, resulting in excessively slow inter-ictal activity in migraineurs, particularly as an attack approaches. The most noteworthy finding was an association between headache intensity and increased delta power (high-intensity attacks showing slower activity in the EEG, in all cortical areas). They found that delta activity increased before pain onset on the affected side and that overall relative theta activity was higher in migraineurs than in controls. It is also important to stress that study subjects did not use migraine prophylactic drugs or other neuroactive drugs like anticonvulsants [8, 9].

In a longitudinal, controlled study, the same group more recently [10], also documented changes in alpha rhythm upon increased migraine load, even when the QEEG was not influenced by recent or imminent attacks.

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In my opinion, the paper presented here deserves to be read by TJHP's readers above all because it stresses the concept of a brain dysfunction in migraineurs between attacks. The only limitation of the study may be the small number of patients considered (33 migraineurs and 31 controls).

As for the reactions to and reflections on our reports [2–6], we must bear in mind that the stigma attached to epilepsy goes back a long way in time and has permeated numberless cultures. In ancient and primitive societies, epilepsy was often believed to originate from malignant causes and to be associated with sin or demonic possession. I personally believe that this stigma may explain a general reluctance (not only in the general public, but even among physicians) to recognise the few documented cases [2, 6] in which migraine/headache has been demonstrated as sole ictal manifestation of epilepsy. As regards the forthcoming revision of the ILAE classification, I suggest that the new term "ictal epileptic headache" be included in a new section called "autonomic epilepsy", as recently proposed for the "Panayiotopoulos syndrome").

In accordance with the inter-ictal neuronal dysfunction in migraine suggested by Marte Helene Bjørk et al., our recent reports stress how cortical spreading depression (CSD) and an epileptic focus may modify, or even give rise to each other [4, 5], even though headache and epilepsy are known to be caused by complex and different pathophysiological mechanisms.

A migraine/headache attack may originate at different cortico-subcortical levels [11] as a result of either cortico-subcortical spreading depression (there seems to be a hierarchical organization with cortical and subcortical areas that are more or less prone than others to develop CSD) [4] or other subcortical networks (such as periaqueductal gray matter, hypothalamic nuclei) [11] which in turn lead, through common final pathways, to trigemino-vascular system (TVS) activation or to the involvement of subcortical networks that modulate the central trigeminal pain pathway [11–13]. These findings are supported by brain imaging studies on migraine that point to the importance of both cortical and sub-cortical structures in the underlying pathophysiology of this disorder [14].

A seizure originates at the cortical level and is modulated exclusively at the subcortical level. Exceptionally, however, an epileptic focus arising from silent cortical areas might be able to activate the TVS, thereby resulting in a migraine/headache with no other known cortical epileptic signs or symptoms [5]. I wish to suggest yet another mechanism, which has been described in relation to the Panayiotopoulos syndrome (PS) [15]: a subliminal cortical epileptic focus might trigger a migraine attack by causing TVS activation. Indeed, ictal epileptic autonomic symptomatology in PS appears to pertain to any epileptogenic cortical onset zone, be this occipital, fronto-temporal or frontal [15]. Central autonomic networks are likely to have a lower threshold to epileptogenic activation than those that produce focal cortical semeiology. Thus, seizures might remain purely autonomic if ictal neuronal activation of non-autonomic cortical areas fails to reach the symptomatogenic threshold [15].

Furthermore, while unequivocal epileptiform abnormalities usually point to a diagnosis of epilepsy, it should be borne in mind that the lack of a clear epileptic spike-wave activity is frequent in other ictal autonomic manifestations [16] as well as in patients with a deep epileptic focus arising, for example, from the orbito-mesial frontal zone [17–19]. In such cases, ictal epileptic EEG activity may be recorded either from the scalp or by stereo-EEG recording as a "theta" or even "delta" shape without any spike activity. The neurobiological reasons for these EEG features related to an ''autonomic epileptic event'' (or deep epileptic focus) probably depend on the age of the patient (the younger the patient, the more autonomic the semeiology), size of the epileptogenic zone, velocity, type, pathways and manner of propagation. These characteristics are, in my opinion, closely related to the anatomo-neurophysiological variables (fiber size, myelination and extent of polysynaptic interconnections).

Both the article by Marte Helene Bjørk et al. and this invited commentary should reassure patients who worry about the consequences of a possible link between headache/migraine and epilepsy, two conditions that may even overlap completely. It should not, however, discourage us from choosing, if necessary, the right anticonvulsant treatment in an attempt to prevent some headache/migraine subjects from joining that minority of patients in whom the lack of therapy may lead to a chronic condition in which headache become drug-resistant.

There is no need to be afraid of a possible link between headache and epilepsy, whereas we do need to be afraid of our ignorance regarding when, how and why headache and epilepsy may on very rare occasions overlap! Rigorous, well-designed studies such as the one by MH Bjørk et al. are a welcome means of advancing our knowledge in this field.

Conflict of interest None.

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